

At page 22, line 28, "MSE" is a part of the tradename "Sanyo MSE MicroCentaur" centrifuge. At page 18, lines 2-3, the abbreviations "SNAFL" and "SNARF" are the tradenames for fluorescent dyes. At page 23, line 9, the abbreviation "COPI" is the name given to the device in Figure 5A and does not have another meaning. At page 11, line 28-29, HSG-IMT VAMP is the tradename of the micropump. Finally, at page 21, line 19, the abbreviation "Pt" is the commonly accepted two letter abbreviation for "platinum".

Applicants believe that these terms have been appropriately clarified.

Declaration under 37 C.F.R. § 1.131

Enclosed herewith is a declaration submitted under 37 C.F.R. § 1.131 by all of the inventors to the application along with Exhibits to the declaration. The declaration demonstrates that the invention of claims 16, 22, 23, 24, 25 and 26 was reduced to practice prior to the publication date of the cited reference U.S. Patent 5,804,436 by Okun et al. All of the inventors have executed the declaration, except for inventor Andersson. Inventor Andersson's executed declaration will be submitted upon receipt.

Rejection under 35 U.S.C. §112

Claims 16 and 22 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. In light of the above amendments, applicants believe that this rejection is now moot and respectfully request that it be withdrawn.

Claim 16 has been amended to delete the term "is capable of flowing in the microfluidic device to" and to amend the claim to positively state that the method comprises applying into the microfluidic device at least one cell which flows into a first inlet flow path.

Claim 22 has been amended so that it is now dependent upon claim 16.

Accordingly, withdrawal of this §112 rejection is respectfully requested.

Rejection under 35 U.S.C. §103(a)

Claims 16, 18, 22 and 23-26 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Okun et al (US Patent 5,804,436) taken with Tracey et al or Wilding et al. This rejection is respectfully traversed for the following reasons.

Okun et al., U.S. Patent 5,804,436 ("Okun"), was filed on August 2, 1996 and issued on September 8, 1998. The instant application was filed on May 16, 1997, less than one year before the Okun filing date. Applicants enclose a Declaration Pursuant to 37 C.F.R. §1.131 of all of the inventors which demonstrates that the invention of claims 16, 22, 23, 24, 25 and 26 was reduced to practice prior to August 2, 1996. Accordingly, Applicants submit that the Okun reference is not prior art with respect to claims 16, 22, 23, 24, 25 and 26, and respectfully request that this rejection, as it pertains to Okun, be withdrawn.

With respect to claim 18, Applicants note that Okun does not disclose the use of stopping the flow of cells while the cells are in the detection zone. In other words, Okun does not describe a stop flow method for evaluation of cell response to an agonist. A stop

flow reaction cell can be defined as one in which reagents, or reagents and cells, are brought together in a flowing stream. Upon contact within the region of mixing, the flow is stopped and the reaction allowed to progress. Detection is performed at the point of mixing and the kinetics of the reaction can be followed. When individual cells are brought to the mixing point, the kinetic response of a specific cell can then be followed from initial to final state, before the next cell is mixed, reacted and studied.

The system described by Okun would not be able to perform this form of data collection. Instead, cells and reagents are mixed in a mixing zone, allowed to react for a controlled period of time in the reaction developing line and then delivered through the detection zone. In such a system, the reaction kinetics of an individual cell cannot be followed. Okun does not disclose the method of observing the effect of one or more candidate compounds on cells in a microfluidic device as is claimed in the instant invention.

At column 5, line 17 and lines 60-65, Okun discloses a steady flow of cells and reagents and a steady flow through the detection zone. The time delay mentioned in column 13, lines 40-45, is the time delay in the reaction developing line, not a time period within the detection zone. Accordingly, Okun does not teach or suggest the claimed method of observing the effect of one or more candidate compounds on cells in a microfluidic device.

Tracey et al. disclose a micro machined device and techniques used to assess cell deformability. Tracey et al. present results for red blood cells only and merely speculate that such microchip based fluidic filter devices could be used with leukocytes. They do not describe any procedures necessary to perform the methods of the claimed invention. They

do not describe chemical forms of red cell analysis but only physical measurement of cell rigidity through a measurement of cell flow rates. Thus, Tracey et al. do not disclose the claimed methods of observing the effect of one or more candidate compounds on cells in a microfluidic device.

Wilding et al. shows the use of micro machined channels. However, the devices described are all straight line channels, without branching and without fluidic networks. At page 47, column 1, they merely extrapolate from a straight channel experiment as to the possibility of multi-channel devices. They do not teach how such complex manifolds would be designed, how they would perform or how they might be used. Wilding does not teach or suggest the application of such devices to the claimed method wherein the microfluidic device comprises a main flow path comprising a detection zone, an outlet and at least two inlet flow paths intersecting and merging with the main flow path at or upstream of the detection zone. Accordingly, it would not have been obvious to one skilled in the art that a device with multiple channels would perform in the same manner.

Thus, since Okun is not prior art with respect to the invention of claims 16, 22, 23, 24, 25, and 26, and since neither Tracey et al. or Wilding et al. describe the methods of the same claims, Applicants submit that the combination of Okun in light of Tracey and Wilding does not teach or suggest the invention of claims 16, 22, 23, 24, 25, and 26, and that this §103 rejection is in error. Applicants respectfully request that this rejection be withdrawn.

As noted above, Okun does not teach or suggest the stop flow method of claim 18. Additionally, neither Tracey et al. or Wilding et al. teach or suggest the method of claim

18. Accordingly, Applicants submit that the combination of Okun in light of Tracey and Wilding as applied to claim 18 is in error and that this §103 rejection is in error.

Withdrawal of this rejection as to claim 18 is respectfully requested.

Applicants believe that this application is now in condition for allowance. Early action to that effect is respectfully requested.

Respectfully submitted,

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